CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
IPRODIONE

Chemical Code # 002081, Tolerance # 00399
SB 950 # 293

November 26, 1986
Revised 7/9/87, 11/04/88, 4/25/91, 2/4/92, 10/25/93, 10/20/94, 7/8/96, 10/24/97

I. DATA GAP STATUS

Chronic, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
All record numbers through 1156577 (Document No. 399-191) and all Record Nos. over 900000 were examined. All appropriate titles indexed as of September, 24, 1997 are included in this Summary. Silva, 10/24/97.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

Revised by: Stanton Morris, 11/04/88; Thomas Kellner, 4/25/91;
J. Gee, 2/4/92; C. Aldous 10/25/93, 10/20/94, and 7/8/96; M. Silva, 10/24/97.

Filename: T971024

These pages contain summaries only. Individual worksheets should be reviewed as they may contain additional effects.

TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

NOTE: SEE ALSO SECTION ENTITLED "REPRODUCTIVE TISSUE EFFECTS: MECHANISTIC STUDIES" AT THE END OF THE "REPRODUCTION, RAT" PORTION OF THIS SUMMARY.

****399-136 120861** "Iprodione: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats", (P.R. Chambers, D. Crook, W.A. Gibson, C. Gopinath and S.A. Ames, Huntingdon Research Center Ltd., Huntingdon, England, Report No. RNP 346/920808, 12/15/92). Iprodione, purity 95.7 - 94.5%, was admixed in the feed at concentrations of 0, 150, 300 or 1600 ppm. Mean estimated compound intake from week 1 to week 104 was 6.1, 12.4, and 69 mg/kg/day for males and 8.4, 16.5, and 95 mg/kg/day for females. Ten and sixty Sprague-Dawley rats/sex/group were sacrificed at 52 and 104 weeks, respectively. Study was flagged for meeting potential adverse effects flagging criterion No. 2 as per 40 CFR 158.34. NOEL = 150 ppm (testicular interstitial cell hyperplasia, atrophy or reduced activity of male accessory sexual glands or tissues, adrenal cortical cell enlargement and/or vacuolation: less pronounced changes were minimal hepatocyte enlargement and splenic hemosiderosis). At 1600 ppm, there was a marked treatment-related rise in testicular interstitial cell adenomas (a **"possible adverse effect"**). The DPR review discusses the likelihood that an antiandrogenic effect of iprodione caused the interstitial cell hypertrophy and adenomas as well as regression of testosterone-dependent tissues. **Acceptable**. Kishiyama and Aldous, 9/15/93.

399-126 097489 Protocol for rat combined study, Record No. 120861, above.

399-135 118050 Preliminary report of Record No. 120861, above (no review).

399-130 111529 1-year interim report of Record No. 120861, above. Examined by H. Green and J. Gee, 1/30/92.

399-139 123489 "Combined study with iprodione in rats: Preliminary subchronic data", Huntingdon Research Center (HRC), this cover letter was dated May 13, 1993, (Final report was submitted to U.S. EPA on 1/21/93). This summary of a retrospective histopathological examination of various tissues associated with male sexual function confirmed that findings of testicular interstitial cell hyperplasia, seminiferous tubule atrophy, absent or abnormal spermatozoa in epididymides, prostate atrophy, and seminal vesicles either missing or having reduced secretion, were all apparent in the subchronic feeding study. Definitive treatment effects were seen in this study only at 3000 to 5000 ppm, with an apparent NOEL for histopathology changes in these tissues of 2000 ppm. This study confirms a "possible adverse effect" in this subchronic study, however the apparent NOEL of this study is much higher than that of the current chronic/oncogenicity study. Aldous, 7/7/93.

020, 021, 080, 095, 096 992765, 992763, 056331, 064306, 064307, and 064305, "Chronic Toxicologic and Carcinogenic Study with RP 26019 in Rats", (S.E. Hastings, Rhodia Inc., Hess & Clark Division, Ashland, OH., Report # SEH 76:57, 24 February 1978). RP 26019 (iprodione). Two lots were used. Lot # 46 CA 7507700 with a certified purity of 99.6% and Lot # 9 CA 7331900 with no certification of purity. The test article was administered in the diet to 60 Charles River Sprague-Dawley CD outbred albino rats per sex per group for 24 months at 0 (Wayne Lab Meal), 125, 250, and 1000 (increased from 500 ppm on test day 8) ppm. Interim sacrifices were performed on 5 rats per sex per group at 6 and 12 months. A 5% to 15% reduction in group mean body weights and a 5% to 11% decrease in food consumption at 1000 ppm was noted for both sexes. No treatment-related oncogenicity was reported. **Adverse effects are not indicated**. Chronic NOEL = 250 ppm (based on body weight and food consumption reduction). Oncogenicity NOEL $\geq$ 1000 ppm. **Unacceptable**, not upgradeable (justification for dosing levels). (Initial review by J. Christopher, 8/21/85, by Gee, 7/8/87 and revised by H. Green, 1/28/92, and Gee, 1/31/92)

399-021; 992763; addendum to volume # 399-020, record # 992765 that contains individual histopathological data.

399-080; 056331; addendum to volume # 399-020, record #'s 992764 and 992765 that contains purity of test material.

399-095; 064306; addendum to volume # 399-020, record #'s 992764 and 992765 that contains purity of test material.

399-095; 064307; addendum to volume # 399-020, record #'s 992764 and 992765 that contains the method of analysis of test material in diet.

399-096; 064305; "Three-month Dietary Oral Toxicity Study of 26.019 RP in Rats": This document was submitted as supplemental information to justify doses used in the study at volume # 399-020, record # 992765. This information did not change the unacceptable status of 992765. No worksheet was done (S. Morris, 11/03/88).

CHRONIC TOXICITY, RAT

Data gap is filled: see combined rat, above.

CHRONIC TOXICITY, DOG

399-062 017052 Kangas, L., "52-Week Toxicity Study in Dietary Administration to Beagle Dogs." (Life Science Research, 9/28/84) Iprodione technical, 96.5% purity, tested at 100, 600 and 3,600 ppm in the diet for one year; 6/sex/group; NOEL: 100 ppm, LEL: 600 ppm (apparent bases for the LEL were lipofuscinosis in proximal convoluted tubular epithelium of kidneys, and pallid appearance in adrenal zona glomerulosa, due to fatty vacuolation). Retinal hyperreflection, usually bilateral, typically of "slight" degree, was somewhat more common at 600 and 3600 ppm than in controls and was considered a possible treatment effect (or treatment exacerbation of naturally-occurring changes). Prostate weights were statistically significantly reduced in dose-related fashion at 600 to 3600 ppm. These findings at 600 ppm were marginal changes. Additional characteristic changes at 3600 ppm in both sexes included adrenal cortical fatty vacuolation in zona fasciculata, centriacinar hepatic cord atrophy, and urinary bladder submucosal changes such as granulomas and crystal formation within giant cells. Consistent hematology changes at 3600 ppm included reduced Hb, reduced HCT, and reduced RBC counts. Also, platelet counts tended to be elevated and partial prothrombin time was extended. The original CDFA review identified this study as indicating a "possible adverse effect", however that review did not identify which finding or finding might be pivotal for eventual risk assessment. It appeared that the major reason for so flagging the study was the comparatively low NOEL (100 ppm). The study was re-categorized on 6/21/96 as not indicating an "adverse effect", based upon additional histopathology evaluations, particularly of adrenals, which raised the overall NOEL for the combined dog studies to 400 ppm (see below). Study status has been designated **acceptable since the review by J. Gee in 1986. J. Christopher, 8/16/85; and Gee, 5/13/86. One-liner updated (no new worksheet) by Aldous, 9/10/93. Review with worksheet by Aldous, 6/21/96.

399-073 36692 U.S. EPA review of Record No. 017052, above.

399-131 112985 Kangas, L., "A 52 week dietary toxicity study of Iprodione in the beagle dog", Bio-Research Laboratories Ltd., Senneville, Quebec, 12/20/91, Project No. 84296. Six dogs/sex were dosed with 0, 200, 300, 400, or 600 ppm Iprodione, Batch No. 8906201, purity 96.2% in diet. Since this study was undertaken as a follow-up to the 1984 LSR study, Record No. 017052, parameters measured in this study were limited in part to those necessary to clarify uncertainties regarding the NOEL of the previous study. NOEL for the present study = 400 ppm (elevated adrenal weights in 600 ppm males). The overall NOEL for the 2 dog chronic studies remained 100 ppm, because adrenal histopathology was not assessed in the ancillary study (see 1996 worksheet

about NOEL change to 400 ppm). Aldous, 9/1/93; edited 6/21/96.

NOTE: The registrant submitted a rebuttal document on 2/2/94 [no DPR record number was given, but tracking ID # is SBDR-145255-E], suggesting that the chronic dog NOEL should be 400 ppm instead of 100 ppm. DPR responded by noting that there was no basis for reducing the NOEL for histopathological changes in adrenals without microscopic examinations of the preserved adrenals from the recent dog chronic study (Record # 112985, above). Aldous, 10/19/94. (NOTE: see 1996 updates, based on further histopathology examinations).

**399-172 137514 Kangas, L., [supplementary information to Document No. 399-131, Record No. 112985, "A 52 week dietary toxicity study of Iprodione in the beagle dog", Bio-Research Laboratories Ltd., Senneville, Quebec]. Original report date was 12/20/91 (date of the current amendment is 4/13/95). The new submission includes histopathologic examinations of several tissues including adrenal glands of all control, 400 ppm, and 600 ppm dogs; kidneys of all females; and prostates of all males. There were no treatment effects identified in any of these tissues. An overall NOEL of 400 ppm is supportable for the two dog chronic studies (Record Nos. 017052 and 112985), taken together. It is no longer appropriate to consider these studies to indicate a "possible adverse effect". Aldous, 6/21/96.

ONCOGENICITY, RAT

Data gap is filled (see Combined, Rat above). See also interpretative information in Rec. No. 124036 under "Oncogenicity, mouse", below.

ONCOGENICITY, MOUSE

****399-141 124045** Chambers, P.R., Crook, D., Gibson, W.A., Read, R.M., and Gopinath, C., "Iprodione: Potential tumorigenic effects in prolonged dietary administration to mice", Huntingdon Research Centre, Ltd., Cambridgeshire, 10 May 1993. CD-1 mice, 50/sex/group, were dosed with Iprodione (26019 RP), Batch DA 604, 95.7% purity, in the diet for up to 99 weeks at dose levels of 0, 160, 800, and 4000 ppm. In addition, 15/sex/group were assigned to 1-year interim sacrifice groups. NOEL = 160 ppm [testicular interstitial cell hypertrophy and vacuolation, non-glandular stomach hyperkeratosis (males), centrilobular hepatocyte enlargement (females)]. An equivocal effect supporting the same NOEL in females was a small increase in amyloid deposits in some tissues, which appeared to be dose-related at the upper two dose levels. Liver was a primary target organ, with hepatocyte enlargement, lipidosis, and elevated hepatocellular adenoma and carcinoma incidences commonly observed in high dose mice. Increased luteinization of ovarian interstitial cells and a slight increase in ovarian luteomas were observed in 4000 ppm females. Amyloidosis was more prevalent in high dose males and females than at other doses, and the apparent dose effect seemed particularly apparent in liver, testes, uterus, stomach, duodenum; and to a lesser extent in thyroid, parathyroids, and adrenals. Liver tumors, and interstitial cell changes in testes and ovaries (including luteomas) are considered **"possible adverse effects"**. Changes in the gonadal interstitial cells may have been caused by altered luteinizing hormone levels (see also Record No. 124036). **Acceptable**. Aldous, 7/29/93.

399-140 124036 Bars, B., Blacker, A., and Urtizberea, M. "Discussion document - Iprodione: Carcinogenicity in rodents", Rhone-Poulenc Ag Company, 6/16/93. The evaluation notes elevated testicular interstitial cell (ISC) tumors in male rats in the 1992 study, increased benign and malignant hepatocellular tumors in male and female mice in the 1993 study. The latter study also found several benign luteomas (derived from ovarian interstitial cells), which were attributed to treatment. All of the above findings were limited to respective highest dosage groups. The 1992 rat study also found atrophy or decreased activity in several testosterone-mediated tissues (including testes). The 1993 mouse study found testicular ISC hypertrophy at the 2 higher doses; ovarian ISC luteinization and absent ovarian corpora lutea were noted at the highest dose; and liver changes (centrilobular hepatocyte enlargement and/or vacuolation) were elevated in high dose males and in the two higher doses in females. The changes in gonadal and related tissues were considered by authors to be related to known anti-androgenic effects mediated by interruption of the feedback control of pituitary release of luteinizing hormone (LH). This is very likely,

considering the close structural relationship to the anti-androgen, flutamide, and to a related fungicide for which reproductive study data were recently examined by this reviewer. Liver tumors in mice were consistent with promotional effects, since considerable cytomegaly was evident in the 1993 mouse study. Useful interpretive information. Aldous, 7/26/93.

399-127 097488 Protocol for mouse oncogenicity study, Record No. 124045, above.

399-132 113162 Interim report for 399-141:124045 (no DPR review needed).

399-137 121822 4-page preliminary data for 399-141:124045 (no DPR review of this interim report).

399-022; 992764; "Chronic Toxicologic and Carcinogenic Study with RP 26019 in Mice." (Rhodia Inc., Hess & Clark Research Farm, 3/6/78). Iprodione (purity unknown but greater than 95%) tested at 0, 200, 500 and 1250 ppm in the diet in a 18-month combined study in Carworth CF-1 mice; 60 mice/sex/dose group; 5 mice/sex/group were sacrificed at 6 and 12 months; enlarged livers in males at high dose at 6 months; enlarged livers and spleens in females in all dose groups at 18 months; chronic inflammation of stomach in males and females at 6 months but not at 12 months; increased incidence of hepatocellular neoplasms in males at high dose, ($p = 0.062$); NOEL $\geq$ 1250 ppm; incomplete; UNACCEPTABLE (purity of compound, no stability or homogeneity data for test material in the diets); J. Christopher, 8/23/85 and Gee, 7/7/87.

399-023; 992775; addendum to volume # 399-022, record # 992764 that contains individual histopathological data.

399-080; 56331; addendum to volume # 399-020, record #'s 992764 and 992765 that contains purity of test material.

399-095; 64306; addendum to volume # 399-020, record #'s 992764 and 992765 that contains purity of test material.

399-095; 64307; addendum to volume # 399-020, record #'s 992764 and 992765 that contains the method of analysis of test material in diet.

REPRODUCTION, RAT

399-123 092739 Henwood, S.M., "Two-generation reproduction study with Iprodione Technical in rats", Hazleton Laboratories America, Inc., Madison, WI, April 29. 1991. Laboratory Project ID: HLA 6224154. Iprodione Technical, purity 96.2%, was administered in the feed at concentrations of 0, 300, 1000, or 3000 ppm (decreased to 2000 ppm at first mating time for F1a rats for the balance of the study) to 28 Crl:CD BR/VAF/Plus rats/sex/group (2 litters each for F0 and F1 generation). Systemic NOEL = 300 ppm (body weight and food consumption decrements in females). Reproductive effects NOEL = 1000 ppm (consistently decreased live litter sizes, partially attributable to stillbirths; low pup weights throughout lactation; pups were often slow moving or hunched at 2000 ppm or above). In addition, changes limited to 3000 ppm included decreased pup survival during early (postpartum days 0-4) and late (postpartum days 14-21) lactation periods. Pup losses appear to have been related to poor nutrition in many cases. Treatment-related clinical signs limited to 3000 ppm group pups included unkempt hair coat, brown material around eyes or nasal area, and tremors. Study is **acceptable, with **no adverse effects**. Kishiyama and Aldous, 10/25/93.

399-114 090536 A letter advising CDFA that a "possible adverse effect" notification had been sent to U.S. EPA regarding study 399-123 092739, above.

399-009; 992772; "Influence of 26 019 RP on the Reproduction of the Rat (3 Generation Study)." (Institut Francais de Recherches et Essais Biologiques (IFREB), 10/13/76) Iprodione (90%) tested at 0, 125, 250 and 1000 ppm in the diet weeks 1 - 5, then increased to 250, 500 and 2000 ppm in a 3-generation, 1 litter/generation

study in Sprague-Dawley rats; 10 males and 20 females/dose group; decrease in F2 litter size (0.1> p >0.05) at 1000 ppm; decrease in food consumption at weeks 1-13, body weight (10%) at week 13 in F2 breeders in all dose groups; decrease in weaning weights (0.1>p>0.05) in F3 litters at 1000 ppm; decrease in litter size and weaning weights through generations at 1000 ppm (2000 ppm); UNACCEPTABLE; (no justification of dose, no histopathology on adult parental animals of high dose and controls). J. Christopher, 8/15/85 and Gee, 7/7/87.

399-080; 50596; addendum to volume # 399-009, record # 992772 that contains the rebuttal, calculation of dose of iprodione in mg/kg body weight and analysis of diet for content and stability.

REPRODUCTIVE TISSUE EFFECTS: MECHANISTIC STUDIES

NOTE: Record No. 147691 found iprodione to be a comparatively poor ligand for the rat prostate androgen receptor. Some metabolites, including RP 25040, had a much greater affinity for the receptor. When effects of iprodione and its metabolites on hCG-stimulated secretion of testosterone in Leydig cell cultures were measured (Record No. 147693), iprodione proved to be an important inhibitor, whereas metabolites such as RP 25040 were ineffective. If the primary mechanism is a perturbation of testosterone secretion, then it would be relevant to address why high iprodione doses led to decreases rather than compensatory increases in circulating levels of LH and FSH. Aldous, 7/8/96.

399-179 147691 Fail, P.A., S.A. Anderson, and S.W. Pearce, "Toxicity testing of a fungicide, Iprodione, in adult male CD Sprague Dawley rats", Laboratory of Reproductive Endocrinology, Research Triangle Institute, 10/24/94. The study had two primary parts: in vitro androgen receptor binding studies, and in vivo studies, including plasma hormone assays and histopathology. Receptor binding studies found iprodione to possess inconsequential binding affinity to the rat ventral prostate androgen receptor. Some iprodione metabolites showed weak but measurable affinity (ca. $1/10^4$ of the binding affinity of dihydrotestosterone). In the primary in vivo study, 18 males/group received either 600 mg/kg/day iprodione or 150 mg/kg/day flutamide (an antiandrogenic drug) by gavage for 30 days. Due to reduced food consumption in treated groups, there were two control groups (18/group, same schedule): untreated, and pair fed (to iprodione). Major endpoints were organ weights and histopathology (liver, adrenals, and reproductive tissues), and levels of plasma reproductive hormones. Levels of testosterone, LH and FSH were assayed over a 10-hr period in cannulated rats. Estradiol could only be measured from a larger blood sample at termination. The iprodione dose was an MTD, based on at least 3 deaths probably due to treatment. There was no clearly treatment-related iprodione effect on plasma hormone levels assayed over time, whereas flutamide rats displayed substantial increases in all hormones assayed, including a several-fold increase in estradiol. In contrast, iprodione rats and their pair-fed controls had remarkably reduced testosterone levels compared to untreated controls. Iprodione rats had slightly (not-significantly) more pulses of LH secretions than did the pair-fed controls, considered to be a possible treatment effect. A small but statistically significant increase in plasma estradiol in iprodione rats compared to ad lib. or pair-fed controls was considered to be a possible treatment effect. Thus, effects of iprodione on assayed hormones were equivocal or marginal; even at the MTD. Iprodione led to reduction of weights of several reproductive structures, most notably in seminal vesicles, well beyond the reduction attributable to pair-feeding. There was no associated histopathology in reproductive tissues of iprodione rats, except for changes also evident in pair-fed controls. Iprodione caused centrilobular hepatocellular hypertrophy and cytoplasmic vacuolization of the zona fasciculata of the adrenals, consistent with other rat studies. Flutamide, however, caused testicular interstitial cell hyperplasia, seminiferous tubule degeneration, and atrophy in prostate and seminal vesicle tissues. Thus, despite the structural relationship of iprodione to antiandrogens such as flutamide, the characteristic effects in reproductive tissues which were strongly evident in the 1992 iprodione rat combined study (Record No. 120861) were generally not evident under conditions of this study. This review includes a comparison of major reproductive tissue findings in the 1992 rat combined study and the 1991 reproduction study with the present data. It is concluded that the present study does not identify a mechanism for reproductive effects (including testicular interstitial cell tumors) in aged rats. Aldous, 7/2/96.

399-181 147693 Benahmed, M., "Effects of Iprodione and its metabolites on testosterone secretion in cultured Leydig cells", INSERM Unite 407, Laboratoire de Biochimie - Batiment 3 B, Centre Hospitalier Lyon-Sud, Pierre

Benite, France, 7/13/95. Investigators tested influence of iprodione and 5 metabolites on testosterone secretion in porcine Leydig cells stimulated by hCG. When cells were incubated with iprodione or metabolites for 3 days, iprodione and 2 metabolites (RP 36115 and RP 32112) caused significant inhibition of hCG-stimulated testosterone secretion at 1 mg/ml, and maximal inhibition at 3-10 mg/ml. Other metabolites (RP 25040, RP 32490, and RP 36118) did not inhibit secretion at any concentration tested (up to 10 mg/ml). When cells were incubated with 10 mg/ml of iprodione or either of the inhibitory metabolites for 2 days prior to addition of up to 3 ng/ml of hCG (normally capable of stimulating about 4-fold increase in testosterone secretion), all 3 test compounds completely eliminated any hCG stimulation of testosterone secretion. A 24-hr incubation with 10 mg/ml iprodione caused about 80% inhibition of testosterone secretion upon hCG stimulation, however this effect was fully reversible after washing of cells and 72-hr culturing in iprodione-free medium. The time of incubation with iprodione required to inhibit hCG-stimulated testosterone secretion was short: there was no essential difference between effects of a 3-hr vs. a 72-hr incubation in the inhibitory effect. Iprodione and ketoconazole ("a well-characterized inhibitor of steroidogenesis") elicited comparable patterns of inhibition of hCG-stimulated testosterone secretion. Investigators anticipate further tests to determine the biochemical mechanisms of action. Aldous, 7/8/96.

TERATOLOGY, RAT

** 399-079 048637; "Iprodione (Technical Grade): Teratology study in the rat." (Life Science Research, England, Report #85/RHAO64/765, 5/28/86). Iprodione (94.2%) in 0.5% w/v methylcellulose was tested at 0, 40, 90 and 200 mg/kg/day by gastric intubation from day 6 to day 15 inclusive gestation in Sprague-Dawley CD rats, 20 rats/dose. Toxicity was only observed at 200 mg/kg/day in fetuses; decrease in fetal size; increase in space between body wall and organs; incomplete ossifications in head, rib cage, vertebral columns, limbs and pelvic girdles. Maternal NOEL $\geq$ 200 kg/mg/day. Developmental NOEL $\geq$ 200 kg/mg/day. **No adverse effect; acceptable.** Dose selection is justified by the pilot study, Record No. 48636, in which clinical signs were noted at 120 mg/kg/day with significant findings at 240 mg/kg/day. The initial review considered the developmental NOEL to be 90 mg/kg/day but all parameters at the high dose were within the range of historical values and there were no clear dose responses. The initial review did not note an adverse effect and reconsideration concurs. Choy, 1/24/86; Gee and Parker, 7/13/87.

399-079 048636; "Iprodione (Technical Grade): Effects of oral Administration upon Pregnancy in the Rat, Dosage Range-finding Study." (Life Science Research, England, Report #85/RHA063/752, 7/11/86). Iprodione (94.2%) in 0.5% w/v methylcellulose was tested in a range-finding study (for study 399-079 048637, above). Treatment was 0, 40, 120, 240, 400 and 800 mg/kg/day by oral gavage from days 6 through 15 of gestation in Sprague Dawley CD rats; 6 female rats/dose with extra 8 at 40 and 800 mg/kg/day. Toxicity observed at 120 mg/kg/day and became significant at 400 mg/kg/day and above; decrease in body weight; increase in clinical signs; decrease in litter size; small and large placenta; increase histopathological findings in fetuses; abnormal skeletal structure; retarded and incomplete ossification. NOEL = 40 mg/kg/day (maternal clinical signs at 120 mg/kg/day); acceptable as a dose range-finding study. Choy, 11/21/86.

399-009; 992767; "Study of the Teratogenic Activity of the Product 26 019 RP by Oral Route in the OFA Rat." (Centre de Recherche et d'Elevage des Oncins, 2/5/75) Iprodione (100%, batch GD 5 740) tested at 0, 100, 200 and 400 mg/kg/day by oral gavage from day 5-15 inclusive of gestation in Sprague-Dawley OFA rats; 25-30 females/dose group; decrease in maternal body weight gain at doses of 100 mg/kg/day and above; decrease in food consumption at 400 mg/kg/day; Decrease in implantation/dam and live fetuses/litter at 400 mg/kg/day; increase in late resorption at 400 and 200 mg/kg/day; apparent NOEL < 100 (maternal body weight gain); teratogenicity data fragmentary; UNACCEPTABLE; not upgradeable (not enough pregnant females in low and high dose groups, no analysis of dosing solutions, no justification of dose, incomplete necropsy data). J. Christopher, 8/14/85.

Supplemental Study:

191 156577 “Iprodione: Toxicology Study in Pregnant Rat by Gavage to Examine Sex Differentiation,” (Repetto-

Larsay, M., Rhone-Poulenc Agrochimie, Sophia Antipolis Cedex; 6/9/97). Iprodione technical (971 g/kg purity) was administered by gavage to mated Sprague Dawley Crl: CD (SD) BR rats (25/dose) at 0 (methylcellulose 400; 0.4%), 20, 120 and 250 mg/kg/day throughout days 6-19 of gestation. Flutamide (50 mg/kg/day) served as a positive control. The purpose of this supplemental study was to test the effects of iprodione on sex differentiation or on anogenital distance of male fetuses when administered to pregnant females during critical periods of gestation. **Maternal NOEL = 20 mg/kg/day** (Nine of 25 dams at 250 mg/kg/day died or were killed in extremis prior to study termination. Clinical signs were prostration, reduced motor activity, facial and urogenital staining. At 120 mg/kg/day, 3 females had dirty fur on facial and urogenital area, starting from gd 19-20. At $\geq$ 120 mg/kg/day body weights were statistically significantly reduced during all treatment periods. In addition, at $\geq$ 120 mg/kg/day the corrected body weight change was significantly decreased but not related to changes in gravid uterine weight. At $\geq$ 120 mg/kg/day food consumption was significantly decreased days 16-20 and at 250 mg/kg/day, food intake was also decreased days 12-16. At $\geq$ 120 mg/kg/day food efficiency was significantly decreased from days 9-12 and days 16-20. At 120 and 250 mg/kg/day, adrenals were enlarged in 7 and 20 animals, respectively.)
Developmental NOEL = 20 mg/kg/day (Body weights in both sexes were significantly decreased at 250 mg/kg/day. There was an increase in runts in both sexes at > 120 mg/kg/day and in edema at 250 mg/kg/day.) **No adverse effect indicated. This study is supplemental.** M. Silva, 10/22/97.

TERATOLOGY, RABBIT

** 399-075; 39606; "A teratology study in rabbits with Iprodione" (WIL Research Labs, Ashland, OH. 12/12/85). Iprodione (95%), 0, 20, 60, 200 mg/kg/day by oral gavage on 6-18 days of gestation; Maternal NOEL = 20 mg/kg/day (decreased weight gain and abortion at 200 mg/kg/day only); Developmental NOEL > 200 mg/kg/day; ACCEPTABLE; no adverse effect. Parker, 7/24/86.

399-009; 992766; "Study of the Teratogenic Activity of the Product 26 019 RP by Oral Route in the Rabbit." (Centre de Recherche Et D'Elevage Des Oncins, 9/28/73). Iprodione (100%) tested at 0, 100, 200 and 400 mg/kg/day by oral gavage from day 6-16 of gestation in New Zealand rabbits; 15-17 females/dose group. Decrease in maternal body weight gain at 200 and increase mortality at 400 mg/kg/day; early, late and whole litter resorption at 200 mg/kg/day and above; **possible adverse effect**; embryonic and fetal death; LOEL = 200 mg/kg/day; NOEL = 100 mg/kg/day; UNACCEPTABLE; not upgradeable (only two dose points as high dose was too high, no necropsy of dams, no clinical observations, no analysis of dosing solutions.) Christopher, 8/14/85.

The two teratology studies are inconsistent in their findings. The early report (009, 992766) showed teratogenicity at 200 mg/kg/day but it was an incomplete study with major deficiencies in several measured parameters. The recent report (075, 39606) is an acceptable study and developmental toxicity was not observed at 200 mg/kg/day. Iprodione is therefore considered not to have an adverse effect in the rabbit. Choy, 11/86

GENE MUTATION

Microbial Systems

** 121 96435 Lawlor, T. and Valentine, D. "Mutagenicity Test on Iprodione (Technical) in the Salmonella/Mammalian-Microsome Reverse Mutation Assay with Confirmatory Assay" (Hazleton Laboratories America, Inc., HLA # 11092-0-401R, 3/7/90). Iprodione, RP-26019, Lot # 89062 01, 96.2% pure, was tested with

Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538, with and without metabolic activation by aroclor-stimulated rat liver S-9 fraction with 3 plates/strain/dose/test condition in 2 experiments; dose levels with S-9 were 0 (DMSO), 10, 50, 100, 500, 1000, 5000 ug/plate and 0, 1, 5, 10, 50, 100, 250 ug/plate without S-9. No adverse effects were noted (no increase in the number of revertant colonies); ACCEPTABLE. (Kellner and Gee, 4/22/91).

399-095; 64259; "In-vitro mutagenicity study in Salmonella typhimurium (Ames' strains) and in Saccharomyces cerevisiae (Zimmermann's strain D7)"; Centre Nicole Grillet, Vitry-sur-Seine, France; 06/28/79. Iprodione, purity not stated; reverse mutation assay in Salmonella tester strains TA 1535, TA 1537, TA 98, and TA 100 carried out with 3 replicates / dose using plate incorporation test without S9 at 0, 1, 10, 100, or 1000 ug / plate or with or without S9 at 0, 12.5, 25, 50, 100, or 250 ug / plate or spot test at 1000 ug / plate; mitotic non-reciprocal conversion, reciprocal recombination, and reverse mutation assays in Saccharomyces at 0 or 250 ug/ml without S9. No dose-related changes seen in revertants, convertants, or recombinants; adequate positive controls; no adverse effect indicated; UNACCEPTABLE study but upgradeable with submission of purity of test compound; Morris, 9/15/88.

399-080; 56333: This is a summary of "In vitro Mutagenicity study in Salmonella typhimurium (Ames' Strains) and in Saccharomyces cerevisiae (Zimmerman's strain D7)" (document # 399-095, record # 64259).

399-009; 31102; "Mutagenicity Testing on Glycophene in Microbial Systems." (Institute of Environmental Toxicology, 7/1/76). Iprodione (99.4%) tested at 0, 10, 100, 500 and 1000 ug/plate with and without Aroclor 1254 induced Sprague-Dawley rat liver S9 activation in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100; 2 plates/group; a host-mediated study was also included in this report using 6 male mice/dose group treated by gavage with 0, 500 or 1000 mg/kg in 2 equal doses over 24 hours; UNACCEPTABLE; not upgradeable (no dose justification, insufficient number of replicates, no repeat trial). Christopher, 8/15/85 and Gee, 7/8/87.

399-009; 31103; addendum to volume # 399-009, record # 31102 that contains reverse mutation assay with liver activation system.

399-009; 31104; addendum to volume # 399-009, record # 31102 that contains host-mediated assay.

Mammalian Systems

399-069; 34272; "CHO/HGPRT mammalian cell forward gene mutation assay." (Pharmakon, 1/3/85) Iprodione (97.3%, lot 83024-01); CHO were exposed for 5 hours in serum-free medium to 0, 5, 10, 50, 75 or 100 ug/ml without S9 and 100, 250, 500, 1000 or 1500 ug/ml with S9; no evidence of mutation induction; UNACCEPTABLE (no repeat trial); Gee, 5/13/86 and 7/8/87.

080; 50597; addendum to volume # 399-069, record # 34272 that contains purity of test material.

CHROMOSOME EFFECTS

** 399-069; 34271; "CHO metaphase analysis: In Vitro chromosome aberration analysis in Chinese Hamster Ovary cells (CHO)." Pharmakon Research International, 1/3/85, PH 320-BO-001-84) Iprodione (97.3%); exposed 5 hours at 0, 15, 75 or 150 ug/ml without S9 and 0, 40, 150 or 400 ug/ml with S9 followed by 14-18 hours of growth; one harvesting time; no evidence for aberrations due to a.i.; ACCEPTABLE. Initially reviewed as unacceptable based on missing purity of test article. This was submitted as Record No. 050598 in 399-080 along with a rebuttal. This submission provides for the upgrading to ACCEPTABLE. Gee, 5/13/86 and 7/8/87.

399-080; 50598; addendum to volume # 399-069, record # 34271 that contains purity of test material.

399-009; 992777; "Dominant Lethal Mutagenicity in Mice." (Rhodia Inc., Hess and Clark, 7/25/74). Iprodione

(purity unknown) tested at 0, 1500 and 6000 ppm fed in the diet for 49 days in a mouse dominant lethal test in Carworth CF mice; 25 males and 50 untreated females/dose group; males mated for 6 days, twice, at 1 male: 2 females; UNACCEPTABLE not upgradeable (no purity of compound, no positive or historical control, males not exposed through the full cycle of spermatogenesis before mating, justification of dose level, improper route of exposure). Christopher, 8/15/85.

399-178 147689 Proudlock, R.J. and E.A. Elmore, "Iprodione mouse micronucleus test", Huntingdon Research Centre Limited, 8/17/94. HRC Study Report No. RNP 442/941483. CD-1 mice, 5/sex/dose/interval, were dosed once by gavage with 0, 750, 1500, or 3000 mg/kg iprodione in 1% methylcellulose, then sacrificed at 24, 48, or 72 hr after dosing. (A dose of 4000 mg/kg had proved lethal to 3/4 mice in toxicity testing). Femur bone marrow smears were evaluated for micronuclei in 1000 polychromatic erythrocytes/mouse. Mitomycin C was the positive control. The high dose of iprodione indicated slight bone marrow depression (assessed by a decreased polychromatic/normochromatic erythrocyte ratio at 48 hr in the highest dose group). There was no significant increase in micronuclei. Study is **acceptable. Aldous, 6/26/96.

DNA DAMAGE

** 339-069; 34269; "In Vitro sister chromatid exchange in Chinese Hamster Ovary cells (CHO)." (Pharmakon Research International, 1/3/85, PH 319-BO-001-84) Iprodione (97.3%); CHO exposed for 5 hours with S9 to 0, 5, 50, 100, 200 or 400 ug/ml; without S9 to 0, 5, 10, 25, 50, 75 or 100 ug/ml followed by 24-28 hours in BUdR; no increase in SCE's; ACCEPTABLE. Initially reviewed as unacceptable based on lack of purity of the test material. This has been submitted as #56332 in 399-080, upgrading the study to ACCEPTABLE status. Gee, 5/14/86 and 7/8/87.

399-080; 56332; addendum to volume # 399-069, record # 34269 that contains purity of test material.

399-009; 31101; "Mutagenicity Testing on Glycophene in Microbial Systems." (Institute of Environmental Toxicology, 7/1/76) Iprodione, (99.4%); tested at 0, 20, 100, 200, 500, 1000 and 2000 ug/disk in a Rec DNA repair assay in Bacillus subtilis strains H17/M45; 1 disk/dose; measured diffusion inhibition zone; insufficient information for health assessment; UNACCEPTABLE; not upgradeable (no replicates, no justification of high dose, no activation, no cytotoxicity = no test). Christopher, 8/15/85.

399-069; 34270; "DNA Damage in Bacillus subtilis with Iprodione Technical." (Borriston Lab, 2/9/85). Iprodione (96.8%); wild type and repair deficient strains (rec^-, exc^-, pol^-) were tested ± S9 at 0, 20.6, 61.9, 185.6, 556.7 or 1670 ug/disk; 3 strains were also grown with these concentrations at ug/ml and CFU determined. $D_{37's}$ were compared; positive growth inhibition in selected strains; UNACCEPTABLE (missing data, study problems) Gee, 5/14/86.

NEUROTOXICITY

Not required at this time.